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REVIEW ARTICLE

Nanomedicine at the Bone–Implant Interface: Emerging Strategies for Osteoporotic Spinal Fixation, Osseointegration, and Regeneration

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ABSTRACT

Osteoporosis weakens the bone–implant interface by reducing bone mass, disrupting trabecular microarchitecture, and impairing bone remodeling. In spinal surgery, these changes increase the risk of pedicle-screw loosening, inadequate osseointegration, delayed fusion, and construct failure. Although conventional mechanical approaches can improve immediate fixation, they do not fully address the impaired osteogenic, angiogenic, inflammatory, and antimicrobial microenvironment of osteoporotic bone.

Nanomedicine offers interface-targeted strategies to enhance fixation and regeneration. Nanoengineered implant surfaces, nanotube-based delivery systems, bioactive nanocoatings, nanocarriers, and nanocomposite scaffolds can provide osteogenic cues, localized drug or ion delivery, immunomodulation, angiogenic support, and antimicrobial protection. These functions may improve peri-implant bone formation while limiting systemic exposure to therapeutic agents.

This review examines nanomedicine approaches for osteoporotic spinal fixation, osseointegration, and regeneration, with emphasis on nanoengineered interfaces, local therapeutic delivery, and multifunctional fixation systems. It also discusses key translational barriers, including nanomaterial toxicity, particle or ion release, coating durability, manufacturing reproducibility, and limited long-term clinical evidence. Nanomedicine may complement established surgical and pharmacological treatment by enabling more biologically active and personalized strategies for compromised bone–implant interfaces.

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INTRODUCTION

Nanomedicine at the bone–implant interface is an emerging area of orthopedic research with potential relevance to osteoporotic spinal fixation, implant osseointegration, and bone regeneration. Osteoporosis compromises bone mass and microarchitecture, increasing fracture risk and reducing the stability of orthopedic implants; consequently, inadequate bone formation, implant loosening, and infection remain important clinical challenges. Nanotechnology offers the possibility of tailoring implant surfaces, scaffold architectures, and therapeutic carriers at length scales that resemble aspects of the native bone extracellular matrix. These approaches may improve cellular adhesion, osteogenic differentiation, mineral deposition, and integration between an implant and host bone. Nanostructured materials have therefore been investigated as bioactive alternatives to conventionally passive orthopedic surfaces and constructs [1-3].

Nanomedicine-based strategies can incorporate nanoparticles, nanoscale surface features, and

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targeted delivery systems to provide osteogenic, antimicrobial, or drug-delivery functions at the implant site. For example, hydroxyapatite-based nanosystems may serve as bone-targeted carriers, while antimicrobial nanomaterials, including silver-based formulations, may help limit bacterial colonization when appropriately engineered for safety. Nanostructured titanium surfaces and titania nanotube arrays are also of interest because they can promote bone-cell responses and function as reservoirs for bioactive molecules, potentially enabling local delivery rather than systemic administration. In osteoporotic settings, these capabilities are particularly relevant because impaired osteogenesis can compromise implant fixation and increase the likelihood of treatment failure[4-6].

Despite substantial preclinical progress, clinical translation remains limited by unresolved issues involving nanomaterial toxicity, long-term biocompatibility, degradation and clearance, manufacturing reproducibility, and regulatory evaluation. Future research should prioritize safer and more controllable nanomaterials, clinically relevant models of osteoporotic bone healing, and multifunctional systems that combine osteogenic support, infection prevention, and stimulus-responsive local therapy. Theranostic designs that integrate treatment with imaging or monitoring could further support personalized orthopedic care; however, their clinical value must be demonstrated through rigorous long-term studies. This review examines current nanomedicine strategies at the bone–implant interface and considers their prospects for improving osseointegration, spinal fixation, and regeneration in osteoporotic bone [2, 7, 8].

OSTEOPOROTIC BONE–IMPLANT INTERFACE: PATHOLOGY AND THERAPEUTIC TARGETS

Why Spinal Fixation Fails in Osteoporotic Bone

bone mineral density and deterioration of trabecular microarchitecture reduce the mechanical competence of the bone–implant interface. Increased porosity, weakened trabecular connectivity, and reduced structural integrity diminish pedicle-screw purchase, pull-out resistance, and resistance to cyclic toggling forces. Consequently, patients with osteoporosis face an elevated risk of screw loosening, migration, construct failure, pseudarthrosis or nonunion, and the possible need for revision surgery. These problems reflect both impaired mechanical anchorage at implantation and a reduced capacity for subsequent bone formation and remodeling around the implant [9-11].

Current strategies seek to improve fixation by increasing the amount or quality of bone engaged by the implant and by augmenting the bone–screw interface. Cortical bone trajectory techniques can increase cortical purchase and may improve fixation strength under selected loading conditions. Expandable and fenestrated pedicle screws, often combined with polymethylmethacrylate (PMMA) augmentation, can also improve anchorage in osteoporotic vertebrae. However, selection of these approaches should be individualized because their benefits must be balanced against procedure-related complications, including cement leakage and challenges associated with revision surgery [9, 12, 13].

Adjunctive systemic and local biological interventions may further support implant fixation by improving the osteoporotic bone microenvironment. Pharmacological management of osteoporosis, particularly anabolic therapy with teriparatide, may enhance bone formation, fusion, and implant stability [14]. In parallel, emerging bioengineering and nanomedicine strategies seek to complement mechanical fixation through osteoinductive and antimicrobial surface modifications, local delivery of bioactive agents, and modulation of inflammation, oxidative stress, and bone-cell activity at the bone–implant interface. Nevertheless, these approaches remain largely investigational and should be integrated with preoperative bone-health evaluation, individualized surgical planning, and systemic osteoporosis management [15, 16].

Therapeutic Targets at the Bone–Implant Interface

trabecular microarchitecture, and impaired regenerative capacity, all of which may compromise osseointegration and long-term implant stability. In osteoporotic bone, dysregulated remodeling, altered osteoblast–osteoclast activity, local inflammation, oxidative stress, and inadequate vascular support may contribute to insufficient peri-implant bone formation. Therefore, successful management requires simultaneous consideration of the biological microenvironment and the mechanical requirements of the implant. Nanostructured and bioactive implant interfaces

are increasingly being investigated to provide local biological cues, enhance osteogenesis, and improve implant performance in compromised bone [4, 15].

Bioactive surface modification and local therapeutic delivery are among the most promising strategies for improving osteoporotic implant integration. Titanium implants with titania nanotube arrays can provide nanoscale topographical signals and may act as local reservoirs for osteogenic agents, including simvastatin, thereby improving bone formation and implant stability in osteoporotic models [5]. Additional approaches include local delivery of antioxidant, anti-inflammatory, and osteoinductive agents to modulate the peri-implant microenvironment, reduce oxidative stress, and support osteoblast function [15].Mechanical stimulation may also promote anabolic bone responses and enhance implant integration; however, the loading protocol must be selected according to bone quality, patient characteristics, and implant location [17].

These biological and nanomedicine-based strategies should complement established surgical and systemic interventions rather than replace them. Advanced fixation approaches, including expandable or fenestrated pedicle screws and cement augmentation, can improve anchorage in osteoporotic vertebrae, although cement leakage and revision-related complications must be considered [10, 13]In addition, anabolic osteoporosis treatment with teriparatide may improve bone formation, fusion outcomes, and implant stability while reducing the risk of pedicle-screw loosening [13, 16]. Future studies should prioritize clinically relevant models, individualized treatment planning, and well-designed long-term clinical trials to clarify the safety and effectiveness of combined mechanical, pharmacological, and nanomedicine-based interventions in osteoporotic patients.

NANOMEDICINE STRATEGIES FOR OSTEOPOROTIC SPINAL FIXATION AND REGENERATION

Nanoengineered Implant Interfaces and Local Therapeutic Delivery

Nanomedicine-based strategies for osteoporotic spinal fixation increasingly focus on engineering the bone–implant interface at the nanoscale. Nanoengineered surface features can emulate key aspects of the natural bone extracellular matrix, including collagen-associated nanoscale topography and hydroxyapatite-like mineral cues, thereby potentially improving protein adsorption, osteoblast attachment, proliferation, differentiation, and early matrix mineralization. These effects may be especially valuable in osteoporotic bone, where impaired remodeling and reduced osteogenic activity can compromise peri-implant bone formation. Emerging multifunctional interfaces, including magnetoelectrically responsive and drug-eluting platforms, may further enable externally controllable osteogenic stimulation; however, evidence for these highly complex systems is still largely preclinical and requires cautious interpretation [7, 18, 19]. Local therapeutic delivery represents a complementary approach for increasing the concentration of osteogenic agents at the bone–implant interface while limiting systemic exposure. Titania nanotube arrays can function as nanoscale reservoirs for drug-loaded micelles; a titanium implant system loaded with tetracycline-grafted, simvastatin-containing micelles promoted bone regeneration and osseointegration in both normal and ovariectomized rat models [5]. Hydroxyapatite-based nanocarriers are likewise being explored because of their compositional similarity to bone mineral, cytocompatibility, and capacity to carry therapeutic cargos. Such carriers may be formulated for sustained or locally responsive release, although it is important to distinguish simple local drug depots from actively bone-targeted systems that use dedicated targeting ligands [3, 17]. Despite their potential, nanoengineered implants and local nanocarrier systems remain subject to important translational limitations. Their performance depends on reproducible surface fabrication, stable drug loading, predictable release kinetics, retention of bioactivity, implant mechanical integrity, and compatibility with the complex osteoporotic microenvironment. In addition, long-term safety must address nanoparticle degradation and clearance, local and systemic toxicity, inflammatory responses, and possible off-target effects. Future progress will require standardized characterization, clinically relevant osteoporotic models, robust long-term in vivo studies, and well-designed clinical trials to determine whether these approaches provide meaningful and durable benefits beyond established mechanical fixation and pharmacological osteoporosis management [15, 20]. The principal challenges at the osteoporotic bone–implant interface and the corresponding

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nanomedicine-based strategies are summarized in Table 1.

Nano-Enabled Immunomodulation, Angiogenesis, and Antimicrobial Protection

Nano-enabled approaches may improve osteoporotic spinal fixation by addressing biological processes that are often impaired at the bone–implant interface, including excessive inflammation, insufficient vascularization, and implant-associated infection. Following implantation, the early immune response strongly influences subsequent osseointegration. Nanostructured surfaces and nanomaterial-based coatings can potentially regulate macrophage behavior, favoring a pro-regenerative and anti-inflammatory phenotype rather than prolonged inflammatory activation. For example, titanium oxide nanofiber interfaces containing nano-heterojunctions have been reported to emulate aspects of the local electrical microenvironment and to influence calcium-associated signaling, thereby promoting macrophage polarization toward a phenotype associated with tissue repair and osteogenesis [21]. Although promising, such immunomodulatory effects should be verified in clinically relevant osteoporotic models and under long-term loading conditions.

Adequate angiogenesis is also essential for peri-implant regeneration because newly formed vessels provide oxygen, nutrients, progenitor-cell access, and signaling factors required for bone formation. Nanoengineered materials may support the coupled processes of angiogenesis and osteogenesis through their surface chemistry, topography, electrical properties, and capacity to deliver biological agents. Graphene oxide–collagen composites and dexamethasone-loaded calcium phosphate–collagen constructs have been explored as examples of multifunctional scaffolds that may promote vascular and bone-regenerative responses [22]. In addition, nano-heterojunction-mediated macrophage modulation has been linked to activation of PI3K-associated signaling and increased secretion of proangiogenic mediators, including fibroblast growth factor 2 (FGF2) [21]. However, the balance between proangiogenic signaling, inflammatory regulation, and osteogenesis must be carefully optimized, particularly in patients with compromised bone turnover.

Antimicrobial nanomaterials offer an additional means of protecting osteoporotic implants from bacterial adhesion and biofilm formation, both of which can compromise fixation and bone healing. Nanostructured metals, polymers, ceramics, and composite coatings may provide contact-active or ion-mediated antimicrobial effects while also supporting osteoconductive behavior. Injectable bone cements reinforced with gold nanoparticle-decorated hydroxyapatite/reduced graphene oxide composites have been proposed as multifunctional systems that combine antimicrobial activity with support for bone regeneration [4, 22]. Nevertheless, clinical translation requires comprehensive evaluation of antimicrobial durability, cytotoxicity, nanoparticle release, immunological effects, degradation behavior, mechanical performance, and long-term safety.

Nanocomposite Fixation Systems for Osteoporotic Spine Surgery

Nanocomposite fixation systems are being

Table 1. Osteoporotic bone–implant interface challenges and nanomedicine-based solutions.

Interface challenge	Nanomedicine-based strategy	Expected outcome
Low bone mass and weak trabecular structure	Nanoengineered surfaces; nano-hydroxyapatite or calcium-phosphate coatings	Improved bone–implant contact and implant anchorage
Impaired osteogenesis and bone remodeling	Local delivery of osteogenic drugs, ions, or growth factors	Enhanced bone formation and osseointegration
Inflammation and oxidative stress	Immunomodulatory and antioxidant nanomaterials	Improved peri-implant healing
Inadequate angiogenesis	Proangiogenic nanomaterials and bioactive nanocomposites	Coupled vascularization and bone regeneration
Bacterial adhesion and biofilm formation	Antimicrobial nanocoatings or drug-releasing nanocarriers	Reduced infection risk and preservation of osseointegration

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investigated as adjuncts to conventional approaches for osteoporotic spine surgery, where reduced bone mineral density, impaired trabecular architecture, and delayed healing can compromise spinal fusion and pedicle-screw anchorage. These constructs typically combine structural matrices with nanoscale reinforcements or bioactive phases in an effort to reproduce aspects of the composition and hierarchical organization of bone extracellular matrix. Examples include graphene oxide–collagen systems, polylactic acid (PLA) reinforced with carbon nanotubes, and calcium phosphate–collagen composites loaded with anti-inflammatory agents such as dexamethasone. In principle, collagen- and calcium phosphate-containing matrices may provide osteoconductive cues, whereas graphene oxide and carbon nanotubes can reinforce mechanical properties and influence cell–material interactions; however, their performance depends strongly on composition, dispersion, dose, and scaffold architecture [22, 23]. The proposed biological mechanisms include improved osteoblast adhesion, proliferation, and differentiation; controlled release of osteogenic ions, growth factors, or anti-inflammatory agents; and stimulation of coupled angiogenic–osteogenic responses. Nanocomposite matrices may be loaded with ions such as magnesium, silicon, or strontium, as well as growth factors or platelet-rich plasma, to promote new bone deposition and fusion. Incorporation of selected nanophases, including cerium oxide or silver nanoparticles, has also been proposed to limit excessive inflammation or bacterial colonization. Nevertheless, the biological effect is not inherently beneficial: nanoparticle release, oxidative stress, inflammatory activation, and altered degradation kinetics must be carefully assessed. Therefore, the ideal system should maintain controlled bioactive release while preserving cytocompatibility, mechanical integrity, and predictable degradation in the osteoporotic bone environment [23].

Preclinical evidence suggests that certain nanocomposite scaffolds can enhance bone formation and spinal-fusion outcomes; for example, magnesium-doped hydroxyapatite/collagen constructs supplemented with platelet-rich plasma have achieved solid fusion in animal models. Mechanical reinforcement using carbon nanotubes or graphene-based components may also improve scaffold stiffness and load-bearing capacity, potentially supporting fixation in weak bone. However, such systems should currently be viewed as emerging technologies rather than established clinical substitutes for optimized screw design, augmentation, and pharmacological osteoporosis treatment. Translation will require scalable and reproducible manufacturing, control of nanomaterial dispersion and release, robust mechanical and biological testing, long-term toxicity studies, cost-effectiveness evaluation, and well-designed human clinical trials before their routine use in osteoporotic spinal surgery can be justified [13, 22, 23].

EVIDENCE, SAFETY, AND CLINICAL TRANSLATION

Preclinical Evidence and Evaluation Framework

Preclinical studies provide the essential evidence base for evaluating nanomedicine strategies at the osteoporotic bone–implant interface before clinical translation. Nanoparticles and nanoengineered scaffolds may enhance osteoconduction, osteoinduction, and new bone formation by modifying surface topography, delivering therapeutic cargos, and influencing the local inflammatory environment. Their effects may include regulation of macrophage activity, reduction of excessive inflammation, and promotion of osteogenic cellular responses. Silver nanoparticles, for instance, have been investigated for antimicrobial activity and may also influence inflammatory responses, making them of interest for preventing implant-associated infection while supporting bone repair. However, their biological effects are strongly dependent on dose, size, surface chemistry, ion release, and local exposure duration [2, 7, 24].

Nanoparticle design is therefore a critical determinant of therapeutic performance and safety. Parameters such as particle size, morphology, surface charge, coating, aggregation behavior, biodegradation, and drug-loading capacity can influence cellular uptake, biodistribution, immune interactions, and osteogenic signaling. Well-designed nanomaterials may modulate pathways involved in bone regeneration, including Wnt/β-catenin and BMP/Smad signaling, or provide controlled release of osteogenic ions, anti-inflammatory agents, antibiotics, or growth factors [24, 25]. For implant-associated applications, assessment should also include the interaction between the nanomaterial and substrate, retention of the coating or therapeutic cargo during

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implantation, effects on surface roughness and mechanical behavior, and stability under cyclic loading and physiological exposure.

A robust preclinical evaluation framework should combine in vitro, ex vivo, and in vivo analyses. In vitro studies should assess cytocompatibility, osteoblast and mesenchymal-stem-cell behavior, macrophage polarization, antimicrobial activity, oxidative stress, and controlled-release behavior. Animal models should then evaluate osseointegration, peri-implant bone volume and density, implant pull-out or torque-out strength, histological bone–implant contact, biodistribution, clearance, and local or systemic toxicity. Although animal models are indispensable, their predictive value is limited by differences in anatomy, remodeling rate, immune response, loading conditions, and disease phenotype relative to humans. Translation will additionally require reproducible nanoparticle manufacturing, standardized reporting and characterization, long-term safety assessment, and early consideration of regulatory requirements. AI-guided materials design and additive manufacturing may ultimately support more reproducible and patient-specific nanomedicine platforms, but these technologies also require rigorous validation [2, 8, 20, 26].

Biosafety, Manufacturing, and Clinical Translation

Nanomedicine at the osteoporotic bone–implant interface has considerable potential, but its translation from experimental systems to routine clinical use depends on resolving interconnected biosafety, manufacturing, and regulatory issues. Safety assessment must extend beyond short-term cytocompatibility to include local and systemic toxicity, inflammatory and immune responses, oxidative stress, genotoxicity, hemocompatibility where relevant, and effects on osteoblasts, osteoclasts, and mesenchymal stem cells. Nanoparticle size, shape, surface charge, coating, concentration, degradation, and ion-release profile can substantially alter biological behavior. Silver nanoparticles illustrate this balance: they can provide useful antimicrobial activity, but their therapeutic window may be narrow because cytotoxicity is concentration- and exposure-dependent, particularly when silver-ion release adversely affects bone-forming cells [2, 7, 24].

Understanding nanoparticle pharmacokinetics is equally important for implant-associated applications. Evaluation should establish whether nanoparticles or released ions remain localized at the bone–implant interface, undergo local transformation, migrate to distant organs, persist in tissues, or are eliminated through renal or hepatobiliary pathways. This requires quantitative investigation of biodistribution, biodegradation, clearance, dose–response relationships, and long-term local tissue responses in relevant animal models. For example, in a rat tibial-defect model, silver released from nanoparticle-coated titanium implants was detected in newly formed bone and transformed to silver sulfide nanoparticles, illustrating why chemical fate and tissue-level localization should be assessed rather than inferred from the initial material composition alone [2, 24]. Manufacturing and clinical translation require a reproducible, quality-controlled process that can be scaled without altering nanoparticle size distribution, morphology, surface chemistry, colloidal stability, drug loading, release behavior, or coating adhesion. Good Manufacturing Practice (GMP)-oriented development should define critical quality attributes and process parameters for raw materials, synthesis, purification, sterilization, packaging, and final-product testing [2, 24, 27]. Regulatory evaluation is challenging because nano-enabled implants may combine a medical device with a drug, biologic, or antimicrobial coating, potentially requiring a combination-product pathway. Therefore, compelling preclinical evidence must be followed by adequately powered clinical studies that demonstrate not only early osseointegration or antimicrobial benefit, but also mechanical durability, long-term safety, and clinically meaningful outcomes. Integration with established fixation methods, bone-graft materials, and systemic osteoporosis management is likely to be more realistic than replacing current orthopedic care; however, cost, scale-up complexity, and regulatory uncertainty remain major barriers to widespread adoption [7, 24].

FUTURE DIRECTIONS AND CONCLUSIONS

Nanomedicine at the bone–implant interface offers a promising route to improve osteoporotic spinal fixation, osseointegration, and bone regeneration. By tailoring implant surfaces, nanostructured scaffolds, and local therapeutic-delivery systems, nano-enabled approaches may address several limitations of conventional orthopedic treatments, including inadequate bone formation, poor implant anchorage, inflammation,

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and implant-associated infection. Future materials should be designed to combine osteogenic, angiogenic, immunomodulatory, and antimicrobial functions while maintaining adequate mechanical performance and long-term stability. Optimization of nanoparticle size, morphology, surface chemistry, degradation profile, and drug-release behavior will be essential to achieve predictable biological responses and minimize adverse effects.

A major future priority is the development of smart, patient-specific, and clinically practical nanomedicine platforms. Stimuli-responsive systems capable of releasing therapeutic agents in response to local pH, inflammation, mechanical loading, or temperature changes may enable more precise control of peri-implant healing. Self-reporting materials and integrated sensing technologies may also permit real-time monitoring of implant stability, local inflammation, infection, and bone-regeneration progress. In combination with artificial-intelligence-guided material design, computational modeling, and three-dimensional bioprinting, these advances could support customized implants, scaffolds, and local delivery systems matched to an individual patient's bone quality, defect geometry, and risk of fixation failure.

Despite this potential, successful translation will require a balanced focus on innovation, safety, manufacturability, and clinical relevance. Future studies should use standardized materials characterization, clinically representative osteoporotic models, long-term mechanical testing, and rigorous evaluation of toxicity, degradation, biodistribution, and immune response. Reproducible large-scale fabrication, cost-effective manufacturing, sterilization compatibility, and clearly defined regulatory pathways will also be necessary for practical implementation. Overall, nanomedicine has the capacity to transform management of compromised bone–implant interfaces; however, its clinical value will depend on demonstrating durable improvements in implant stability, osseointegration, and patient outcomes beyond those achieved with current surgical and pharmacological strategies.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest related to the research, authorship, or publication of this manuscript. All authors have disclosed any financial or personal relationships that could potentially influence or bias the work presented.

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